Resistive breathing and respiratory muscle fatigue: A load of concern just expired!

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Phew!

Herein you'll find a puzzle set,

Some issues of intrigue;

Of chief concern—resisted breath

And muscles that fatigue.

When exhaled flow is compromised

Air pumps become deflated;

But load on entry—and surprise!

Some weakness is abated.

So explore now what you will,

Paired stress or isolation;

But be assured that breathing out, still

Provides inspiration!

Much doth change when muscles tire;

But one concern has just expired!

Pulmonary ventilation is a cyclical process of inhalation and exhalation of air providing dynamic tidal exchange between alveolar gas-exchanging units of the lungs and the external environment. During quiet breathing at rest, the twin act comprises active inspiration, with recruitment of muscles that increase thoracic cage volume, complemented by successive passive expiration where muscle

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relaxation and recoil of the elastic lung is sufficient to void waste breath. In circumstances of increased ventilatory demand however, exemplified in exercise, ventilation is achieved by active oscillatory recruitment of inspiratory muscles, and expiratory muscles of the thorax and abdomen. Much has been revealed about the neural substrate for conditional dual oscillator behaviour in rhythm-generating sites of the medulla oblongata of the central nervous system, enriching a long-standing interest in respiratory muscle performance in healthy subjects and patient populations. From a mechanical perspective, the recruitment of abdominal muscles in the late expiratory phase of the respiratory cycle decreases end-expiratory lung volume, lengthens the diaphragm, and raises intra-abdominal pressure, thereby facilitating diaphragm performance and hence tidal volume generation during inspiration. As such, active expiration facilitates increased alveolar ventilation and gas exchange, essential in times of increased metabolic demand.

Loading of the respiratory system, dramatically increases the work of breathing, with a capacity to provide sufficient stress to elaborate respiratory muscle fatigue, with implications for cardio-respiratory physiology. Fatigue of the inspiratory and expiratory pump muscles places considerable limits on ventilatory capacity and aerobic performance, evokes reflex activation of sympathetic vasoconstrictor tone affecting limb muscle blood flow, and elevates the perception of laboured breathing (dyspnoea). The limiting effect of loading and the 'stealing' of locomotor blood flow is relevant to the high performance of athletes and general ambulatory function and quality of life of patients with respiratory disease (Harms *et al*., 1997; Borghi-Silva *et al*., 2008). The powerful effect is readily revealed in reverse by unloading the respiratory muscles, which improves locomotor muscle blood flow and oxygenation both in healthy subjects and diseased patients. Of added interest and intrigue, the physiological consequences of loading, in some circumstances, may relate to coincidental fatigue in inspiratory and expiratory muscles. For example, expiratory resistive loading results both in abdominal and diaphragm muscle fatigue (Taylor & Romer, 2009). The corollary question as to whether inspiratory resistive loading causes expiratory muscle fatigue has hitherto been unaddressed. In this issue of *Experimental Physiology*, an important answer is provided in elegant form by Peters *et al*. 2017.

Healthy young male subjects underwent isocapnic inspiratory resistive loading (IRL; 60% maximal inspiratory pressure at controlled respiratory periodicity) to task failure, the point at which subjects failed to achieve or maintain their respective target inspiratory pressure. Costal diaphragm and abdominal (rectus abdominus and external oblique) muscle function was assessed at baseline and following IRL by assessment of surface electromyogram activities and transdiaphragmatic twitch

pressure and gastric twitch pressure in response to magnetic stimulation of cervical (phrenic) and thoracic spinal nerves.

As expected, IRL resulted in substantive diaphragm muscle fatigue, evidenced by 25-42% reduction in non-volitional, neurally-evoked transdiaphragmatic twitch pressures. Of interest, expiratory muscles were co-activated with the diaphragm during IRL, although recruitment represented a modest increase, and was considerably less than that reported for activity in response to expiratory resistive loading (Taylor & Romer, 2009). However, there was no evidence of abdominal muscle fatigue following IRL, as illustrated by the lack of a significant decline in gastric twitch pressure in response to potentiated magnetic stimulation of the thoracic nerves. Thus, during IRL, expiratory muscles are active in inspiration, but quite surprisingly, IRL does not recruit active expiration. *Curiouser and curiouser!*

Fortuitously, the observation offers additional insight into the underlying mechanism driving cardiovascular effects of increased respiratory muscle work (Dempsey *et al*., 2002). Time-dependent increases in heart rate and arterial blood pressure in subjects studied by Peters *et al*. (2017) can be attributed solely to the finding of fatigue in a subset of respiratory muscles, arising most likely from an exertional metaboreflex in the inspiratory pump muscles. It is convincingly argued by the authors that a two-to-three fold increase in tension-time index of the diaphragm during IRL likely compromised blood flow leading to diaphragm muscle fatigue. The presumed activation of mechanically-sensitive (type III) afferents and metabolically-sensitive (type IV) afferents leads to sympathetic nerve mediated cardiovascular effects (Dempsey et al., 2002). The study by Peters *et al*. (2017) strongly suggests that expiratory muscle fatigue is not obligatory for the manifestation of compromised locomotor blood flow during increased respiratory work (Harms *et al*., 1997). As such, functional coupling of agonist-antagonist respiratory muscle behaviour appears to be more important during expiratory loading compared with inspiratory loading, providing experimental approaches that can exploit the summation or separation of inspiratory and expiratory muscle activation and fatigue during resistive breathing.

Of course, the findings may be peculiar to healthy young male subjects, necessitating validation in other relevant study cohorts, a point acknowledged by the authors. Nevertheless, whatever the outcome of those studies, Peters *et al*. (2017) provide an unexpected observation with implications for the (re)evaluation of published work and future plans. We can draw comfort from the knowledge that indefatigable efforts into the future will continue to explore the ins and outs of this important issue worthy of pursuit!

Conflicts of Interest

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